ASSESSMENT OF CLINICAL AND IMMUNOLOGICAL FAILURE In CHILDREN ON FIRST-LINE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN ADDIS ABABA, ETHIOPIA

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Acronyms

ART: Antiretroviral therapy

AHR: Adjusted hazard ratio

AZT: Zidovudine

BMI: Body mass index

CD4: Cells with CD4 mark

CI: Confidence interval

D4T: Stavudine

EFV: Efavirnez

HAART: Highly active antiretroviral therapy

HAZ: Height-for-age Z-scores

HIV: Human Immunodeficiency Virus

HR: hazard ratio

IRS: immune reconstitution syndrome

LWHA: living with HIV/AIDS

NVP: Nevirapine

NNRTI: Non Nucloside analogue reverse transcriptase

NRTI: Nucloside analogue reverse transcriptase

OIS: opportunistic infections

PMTCT: Prevention of mother to child transmission

SD: standard deviation

UNAIDS: United Nations' Program on HIV/AIDS

WAZ: Weight-for-age Z-scores

WBC: white blood cell count

WHO: World Health Organization

3TC: Lamuvudine

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Abstract

Background: The emergence of resistance to the first line Antiretroviral therapy (ART) leads to a need for more expensive and less tolerable second line drugs. Therefore it is essential to identify factors associated with increased probability of treatment failure.

O**bjectives**: The aim of this study was to assess clinical and immunologic failure of first line treatment failure in children and time of switch to second line drugs.

Method: A retrospective cohort study was conducted with chart review of all HIV-infected children less than 15 years of age, who took HAART for at least six months in the major hospitals of Addis Ababa. Data was collected, entered and analyzed using Epi info version 3.5.1, SPSS version 16 and Smart soft ware 2008. The Cox proportional-hazards model was then used to assess the predictors of factors associated with treatment failure.

Result: A sample size of 1186 children was evaluated. Five hundred seventy seven (48.7%) were male and 609 (51.3%) were female with mean age of 74(±37SD) months. Out of 167(14.1%) children who had treatment failure, 80 (6.7%) had clinical failure, 87 (7.3%) immunologic failure and 18 (1.5%) had both. Patients who had height for age less than -3 z-score(ZS) with adjusted hazard ratio(AHR) of 0.429 95% CI(0.291-0.632) were found to have high probability of treatment failure. Patients with base line CD4 count below 50 (AHR=2.009(1.194-3.380)); with presence of chronic diarrhea after start of ART (AHR= 3.439(1.372-8.623)) and with drug substitution (AHR=1.695(1.053-2.728)) were also found to be at risk. From all treatment failures, only 24(14.37%) of patients were switched to second line with a mean delay of 24±31.67SD month.

Conclusions: Having chronic malnutrition and low CD4 at base line and chronic diarrhea after the start of ART and substitution of drug were found to be predictors of treatment failure in children. Most of the treatment failure were not detected and are not switched to second line

Recommendation: monitoring of children for treatment failure with the above predictors and timely switch to second line is mandatory.

1 Introduction

The HIV epidemic continues to be a major challenge to global health. According to the 2009 UNAIDS report, about 33.4 million people are living with HIV (LWHA) all over the world and out of them 2.1 million are children . In 2008 alone, 430, 000 children under 15 year of age were newly infected and 280, 000 lost their lives because of AIDS (1). Sub-Saharan Africa remains the region mostly affected by HIV; where 90% of new HIV infections among children occurred. Approximately 7 out of 10 deaths recorded were in this region (1, 2).

Despite the fact that the number of children receiving ART globally increased from around 75, 000 in 2005 to almost to 360, 000 in 2009 (3),Pediatric ART still lags behind as children account for only 6% of the total ART patients. Only one in seven of the 780,000 children in need of ART are receiving it (4). Between 2008 and 2009 in sub-Saharan Africa, the estimated number of children receiving ART rose from 224, 100 to 296,000. Total ART coverage was estimated about 26% (5).

In Ethiopia, in 2006 an estimated 134,000 children less than 15 years of age were LWHA; 2009 National pediatric Cumulative patient ever enrolled in HIV care were 29,546 and cumulative ever Started ART are 13,650. Children who were on first line regimen were 10,361, while children on second line were only 135 cases; which showed slight increase from 2005 i.e. 10 cases only (6, 7).

Antiretroviral drugs (ARV) are drugs used lifelong to suppress the viral replication which limit the weakening of the immune system .Taking two or more drugs at a time is known as combination therapy and if combination is three or more, it is referred as to Highly Active Antiretroviral Therapy (HAART)(8).

Many studies report the success of HAART in improving clinical and immunologic outcome of children (9-13). But as the rate of HAART coverage increases, drug resistance with subsequent treatment failure starts to emerge simultaneously. Theses treatment failure in children could be due to clinical, immunological or virological failure (14-16).

1.2. Rationale of the study

Though HAART has resulted decrement in morbidity and mortality (13); keeping patients on such lifelong drug with monitoring of different investigations is extremely expensive in developing countries. Furthermore, the emergence of resistance leads to treatment failure and a need for second line drugs. These second line drugs are said to be more expensive and have increased side effects and decreased tolerability than the first line (14, 17). In addition treatment failure leads to reemergence opportunistic infection with all its consequences of social, economic constrains in the family and to the whole community. Even though it is very costly to shift to second-line ART, late switching to second-line ART is expected to result in greater resistance and may limit the effectiveness of second-line regimens (16).

Therefore, addressing the predictors associated with treatment failure in order to be able to prevent it is very important. However, there is limited data on children who have treatment failure, the associated factors and the timing of shift to second line drugs .This is a concern for subsequent ART management, quality of life and long term outcome of children living with HIV.

2 Literature Review

2.1 Overview of the HAART Impact

Since the introduction of HAART, HIV related morbidity and mortality have noticeably declined (13). The benefits of HAART in promoting growth and maintaining prolonged health have been consistently shown in several studies (9-13). This has been demonstrated by the Ugandan prospective cohort, which showed growth increment increased after 48 weeks of therapy (9). Another study from the Netherlands also showed an increment in weight, height and Body mass index (BMI) (10). In Cambodia and other studies continually revealed Opportunistic Infections (OI), diarrhea and pneumonia are becoming uncommon in the HAART era compared with the pre-HAART era (9-13, 18).

2.2 ART Treatment Failure

Once patients are started on ART, they generally remain on medications indefinitely. A change in the first-line ART regimen is often necessary because of a number of reasons among which first-line ART failure is one. Treatment failure in children can be due to clinical, immunological or Virologic Failure (14-16).

Clinical failure: is defined as either of the following:

1. Occurrences of new Opportunistic infections (OIs) or malignancies or
2. Failure to sustain growth rate in a child who had showed response initially
3. Loss of neurodevelopment milestones excluding other causes (14-16).

If the reason for considering treatment failure is growth failure; nutrition therapy should be insured first. Before labeling clinical failure, it is also recommended that a child with pulmonary or lymph node TB be treated. (14, 16)

Immunologic failure: is defined as arpid rate of decline to at or below to the sever immunodeficiency state for age as seen in Table 1or a fall in CD4 50% of the peak without other conditions or causes (14,16). It is required to have at least two CD4 measurements before defining for treatment failure and switching (14). Generally treatment failure should be differentiated from **immune Reconstitution syndrome** (IRS) which is a paradoxical clinical deterioration while the immune system begins to improve in contrast to treatment failure where immunologic improvement is usually failed to demonstrate(14,19).

Table 1 Age related immunologic classification

HIV associated immunodeficiency	CD4 percentage≤59month or count>59month			
	<11mo	12-35mo	36-59mo	5yrs &above
Not significant	>35	>30	>25	>500
mild	30-35	25-30	20-25	350-499
advanced	25-30	20-25	15-20	200-349
severe	<25	<20	<15	<200 or <15%

Virologic failure: thresholds in children are not yet clear. Levels more than 100,000 copies are required to switch treatment. Routine viral load measurement has not been recommended in resource limited countries unless conflicting correlation b/n clinical and immunologic failure because of the cost and ambiguity of its interpretation (14).

2.3 Magnitude of first-line ART failure

Despite the relatively limited pediatric ART coverage, studies now demonstrate that as more children accessed the antiretroviral treatment, a simultaneous increase in the number of treatment failures occurred, and requiring second-line treatment. A systematic review of first-line ART failure and attrition rates in resource constrained settings revealed different rates of first-line ART failure among studies using clinical criteria only or immunological criteria and those use virology criteria in adult studies (20-22).

2.4 Predictors of treatment failure

There are many factors that increase the likelihood of first-line ART failure. Inadequate adherence to treatment, drug side-effects and toxicity leading to poor adherence to treatment, Socio demographic factors such as age ,sex , being an orphan , baseline patient factors (e.g. high pre-treatment viral load, low pre-treatment CD4 Count, prior WHO staging and drug-drug interactions between the antiretroviral drugs and other concomitantly administered drugs resulting in sub-therapeutic drug concentrations are among the commonest factors increasing the probability of occurrence of first-line ART failure (23-31).

The primary factor associated with poor treatment outcome is in fact poor adherence to treatment which is in turn associated with many factors such as not enough drug at home, caregivers being away; the caregiver's educational status; frequency of visit to the clinic; distance traveled to the clinic; drug formulation, regimen type and duration of HAART usage, financial constrains, missed clinic appointments, child refusal or self-discontinued, and gender (23-27).

Another factor associated with treatment failure is higher initial viral loads and severe immunologic suppression during the start of ART. As the African study demonstrates, a viral load greater than a million copies per ml is associated with virologic failure (32). Studies done in Uganda, South Africa, Thailand and Zambia showed that delay in starting of HAART with severe immunologic suppression is also another predictor of first-line ART failure that should be looked for (20,28) . Therefore, earlier intervention is demanded since mortality during the early days of therapy is high. Most of the deaths recorded within 19 days of ART initiation in Uganda, 5 months in South Africa and three months in Jimma, Ethiopia (20.23, 31).

The other predictors of treatment failure mentioned are age and sex of the child. A cohort study in Thailand showed younger age was found to be predictors for immune recovery (30). In the UK and Ireland though the immunological response is better in younger children, poorer virological response and increasing the risk of resistance was documented (33). Similarly, in the South African and Tanzanian study younger age is associated with virologic failure (28,34). In a study conducted at Makerere University in Kampala the independent predictor documented was male gender similarly the Thailand study showed better immune recovery in female gender (20, 30).

The Cambodia cohort study, including a cross-sectional evaluation of virologic status of 212 who took a 12 month of HAART before the study period showed being an orphan is statically associated with virologic failure (18). Other predictors associated with treatment failure in other studies were inadequate dose adjustment leading to sub optimal dose, drug toxicity with subsequent treatment discontinuation and occurrence of opportunistic infection. Regiment type also has effect as demonstrated in Tanzania study.(34,35) Malawi and Ethiopia studies additionally suggest that chronic gastroenteritis which decreases absorption of the drugs as one of the risk factor for treatment failure (26, 31).

Uganda, Zambia, South Africa , Côte d'Ivoire studies revealed that though the overall immunological and virologic responses are similar in resource limited and resource rich countries; but the CD4 recovery rate and growth responses have been documented to be slow in resource limited countries. This could be because of associated higher background malnutrition, infection rates and long travel times to access care. This suggests that in sub-Saharan Africa there is a need for low price diagnostic tests for earlier identification of HIV infection in infants, improved access to ART programmers, including extension of care to remote areas and the integration of ART programs with other health-care services, such as nutritional support (18, 20, 27, 36 and 37).

2.5 The probability of treatment failure and time of switch

In a South African retrospective cohort study of 151 patients 9.9% have progressed to a second line, one (0.7%) to a third line, and one (0.7%) to a fourth line. Antiretroviral drug resistance was detected in more than 80% of KwaZulu Natal South African patients with a detectable HAART drug resistance which predicts failure of a first HAART regimen (33). The probability of failure after a year of first line ART regimen in Malawi was 1.6% (26).

A south African study using the international epidemiologic databases of 5484 children with median follow up of 16 months reported Virologic failure in 310 children with cumulative probability of (11.4%) , 146 were switched with cumulative probability of 6% at 3 years but 50% of the children with virologic failure were not switched to second-line antiretroviral therapy (ART) and, for those who did receive second-line treatment, a delay of close to five months between failures and switching occurred (28). The retrospective study in Malawi demonstrated the average time on ART before shifting to second-line ART regimen was 16.3 months and of the total 1434 patients who were eligible, only 22 patients (1.5%) were on a second-line regimen due to ART failure. In South Africa the median time between virologic failure and switch is 4.6 months (26).

2.6 Situation of treatment failure in the study setting

Ethiopia's first pediatric HIV/AIDS situational analysis revealed many barriers for the care and support of pediatric HIV patients. Only 28% of pregnant women in Ethiopia have antenatal care with only10% institutional delivery, therefore, diagnosing pediatric HIV infection early and initiation of timely ART is hampered. Antiretroviral therapy started according to National guideline adopted from WHO. Routine virologic examination is limited. Children who are in second line treatment were only 10 in 2005 and currently 135 nationwide (6, 7).

According to a three -year's retrospective Cohort analysis at Jimma University, Ethiopia reported Clinical treatment failure in 6.2% patients and immunologic treatment failure in 11.5% of the patients. Presence of chronic gastroenteritis, appearance of new opportunistic infection after

starting treatment were associated with immunologic treatment failure. Deaths that occurred within the first three months of therapy were associated with higher rate of defaulters, treatment failure, severe drug toxicity and regimen change (31).

Regarding the predictors of treatment failure in an Ethiopian context, detailed studies are rare. The study done in Ethiopian children on adherence to ART in Addis Ababa in five major hospitals, namely Tikur Anbessa Generalized Specialized Hospital, Saint Peter Hospital, Yekatit 12 Hospital, and Zewditu Memorial Hospital showed adherence rate of 93% in the past 3 days and 87% in the past 7 days before the date of interview and it is acceptably higher than other similar setups (22).

3 Objective of the study

3.1 General objective:

The aim of this study is to identify the clinical, immunologic failure of pediatric patients who have been using highly active antiretroviral therapy (HAART) for more than six months in selected Hospitals of Addis Ababa Ethiopia.

Specific objectives:

3.1.1 To determine the magnitude of clinical treatment failures

3.1.2 To determine the magnitude of immunologic treatment failures

3.1.3 To identify predictors of treatment failures

Secondary objective:

To estimate the magnitude of patients with treatment failure but still on first line drug (not switched to second line)

4 Methodology

4.1 Study setting

The study was carried out in Addis Ababa, the capital city of Ethiopia .The city area is 450 square kilometer with estimated 2.7 million populations. The four major public pediatric referral hospitals namely Tikur Anbessa, Yekatit 12, Zewditu Memorial and Alert hospital were selected for this study. Those hospitals were selected because they have been providing ART service for more than a year and a prior pediatric adherence study was done in this setting and furthermore these hospitals are also providing second line ART. A total number of children on ART in these hospitals are greater than 50% (ie 1.732) of the total children in all Addis Ababa public hospitals i.e. 2041(38). ALERT Hospital is under the Federal Ministry of Health. Yekatit 12 and Zewditu Memorial hospitals are under the Addis Ababa Regional Health Bureau, while Tikur Anbessa is under Addis Ababa University.

4.2 Study Design

The study design utilized for this study was a retrospective cohort study.

4.3 Source population

All children under the age of 15years who are on ART and living in Addis Ababa, Ethiopia.

4.4 Study subjects:

The study population was all HIV infected children who started Anti Retroviral Treatment between March 2005 and March 2011 in the four selected hospitals namely, Tikuer Anbessa Specialized, Zewditu Memorial, Yekatit 12 and ALERT hospitals.

4.5 Sample Size

I. For the first objective of this study is the formula for estimating single population proportion given below was used to calculate the required sample size.

$$n = \frac{Z^2_{\alpha/2} P(1-P)}{d^2}$$

Where, **p** is the expected percent of children who have treatment failure and **d** is the absolute precision. In this case, from literatures reviewed, immunologic failure is approximately 11.5%. **p= 0.11** is and assuming **d=0.02**, the required sample size will be 459. Adding a non-response rate for incorrect documentation of records 10% i.e. 46, the calculated sample size by this method will be 505 (31, 39).

Table 2: Sample size Determination

Variables	P	d	Sample size calculated	Total including 10% for improper documentation
Clinical treatment failure	6.2%	2%	248	273
Immunologic failure	11.5%	2%	418	459

II. To determine the required sample size for the second objective which is to determine the predictive factors for treatment failure, the two population proportion formula given below will be used.

$$n_1 = \left[\frac{\mathbf{Z\alpha/2\sqrt{[1 + 1/r]p(1-p)} + Z\beta\sqrt{p1(1-p1) + p2(1-p2)/r}}^{\mathbf{2}}}{\mathbf{(p1 - p2)2}} \right]$$

Where

n1 = the required sample size for the treatment failures with predicting factor

n2= the required sample size for treatment failure with no predicting factors

n1:n2 = 1:3

p1= Proportion of predicting factors in treatment failure

p2= Proportion of absence predicting factor in treatment failure

$$P = \frac{p1 + rp2}{1+r}$$

α= Type-I error (0.05)

Zα/2= Critical value at 95% level of confidence 6

Zβ = standard normal distribution value corresponding to power 84

Table 3: Sample size determination with two proportion sampling method

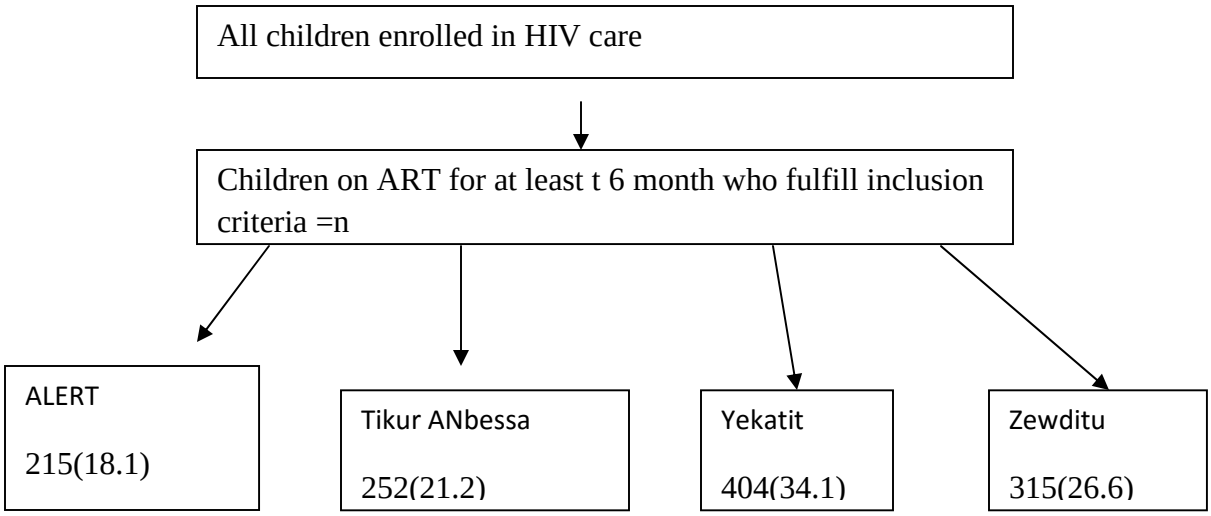
Variable		Sample size for treatment failure with predictors :n	Sample size for treatment failure with no predictors: 3 n	Total sample size including 10% for improper documentation
Proportion Of Adherence in treatment failures	95.0%	**286**	**859**	**1,259**
Proportion Of non Adherence in treatment failure	99.4%			
Proportion of high CD4 in treatment failure	29.9	109	218	360
Proportion of low CD4 in non treatment failure	15.7			
Proportion EFV-based regimen compared in treatment failure	17.5%	127	381	608
Proportion of none EFv based regimen in treatment failure	44.4%			
Proportion of NVP-based regimen in treatment failure	82.5%	84	252	672
None Nvp- based regimen in non treatment failure	(55.6%)			

From the possible common predictors of treatment failure adherence yields the higher number, therefore, sample size of 1,259 was calculated considering the visibility of this study in the allocated time.

4.6 Sampling procedure

The sample was proportionally allocated to each Hospital based on the number of pediatrics ART enrolled patients. Systematic random sampling technique was done at each hospital to identify the study subjects using the ART unique numbers from the registration book. But since the sample size was not reached finally all children who fulfilled inclusion criteria were used, except those with poor documentation See Fig 1.

Figure 1: Diagram for sampling procedure



Inclusion Criteria

- Children who started HAART at least 6 month before the time of the survey
- Children age under 15 years of age since above 15 are referred to adult clinic
- Children taking triple ART drugs
- Children on HAART with at least two follow up visits

Exclusion Criteria:

- Children who took ART only for PMTCT purpose
- Children who don't have two follow up visits after ART

4.7 Data collection Procedures

The sources of data for this study were the Pre-ART register, the ART register and the patients' ART follow up and medical charts. In those registers and follow up charts, clients' socio demographic, clinical and laboratory information, treatments being provided, the follow up status of each client are recorded **(Annex I**). Data was collected using a structured checklist for records review developed from the registers and follow up charts. Since the registers are prepared in English, the checklist is also prepared in English.

4.8 Variables of the Study

4.8.1 Dependent Variable

The dependent variable to be studied is the outcome of first-line pediatric ART in terms of clinical failure and immunologic failure.

4.8.2 Independent Variables

The independent variables of this study are socio demographic factors such as age, sex, care-giver HIV status, whether the child is orphan or not, baseline clinical and laboratory data of patients such as WHO Clinical stage ,CD4 Count or CD4% at the start of ART, adherence level, presence of chronic diarrhea after ART, nutritional status at the start of ART, presence or development of drug-side effects and drug substitution , prior PMTCT drug exposure, drug form, and the ART regimen used.

4.9 Data Management

Data was collected by nurses trained on pediatric HIV care and support, and who have been working in ART clinic of the respective hospitals. They were trained by the primary investigator about the data to be collected from the patient cards through the questionnaire and they were supervised throughout data collection process. The questioner was retested before the actual data collection. The data was collected in the health facilities starting from Dec 2010 to March 2011

until the sample size was saturated. Five percent of the data cross checked for completeness, accuracy, and consistency before entry to software program and accordingly adjustments was made. During data entry double entering was done for 5% of the check lists.

4.10 Data Entry and analysis

The data was entered and analyzed using software programs Epi info version 3.5.1, and SPSS version 16.Anthropometric measurement was analyzed with Smart soft ware version 3.2.2. Descriptive statistics as range, means with standard deviations (SD) were generated and cox regresstion we association between the outcome and the independent variables were taken as significant at p= 0.05. Moreover, treatment failure rate along with 95% CI were estimated. First-line ART failures were described by subcategories of demographic and clinical characteristics. Independent variables that were significantly associated with first-line ART failure in bi-variante analysis were further examined in multivariate analysis. The Cox proportional-hazards model was used to assess the predictors of factors associated with treatment failure. Kaplan-Meier survival methods were used to estimate the probability of treatment failure

4.11 Operational Definitions

Regimen changes: replacement of the first antiretroviral regimen by another in the same regimen

First line ART: is the original drug regimen used as the national guideline with combination of two NRTIs and one NNRTI.

Second-line ART: is the regimen used immediately after first-line therapy.

Switch: Regimen Change from the first line to second line or to third-line.

Substitution: This refers to the replacement of one of the antiretroviral drug by another in the same regimen.

Clinical failure: is defined as having either growth failure ;or developmental delay or regression) or occurrence of new or recurrent WHO clinical Stage IV.

Growth failure: is defined below -3Zscor of NCHS curve any time after 6 month of ART and if this growth failure persists for another six month .Additional six month was used assuming if the growth failure is due to nutritional it can be treated on the next 6 month after treatment failure identified.

Immunological treatment failure: defined as achievement of a CD4 cell percent or count below the cut off level for age (CD4 cell percent; less than one year< 25%, one to five years < 20%, greater than five years <15%) after 24 weeks of HAART or .

The children are classified into: Immunological failure (IF), clinical failure (CF) and both clinical and immunological failure (CF and IF).

Primary care giver – a person responsible for giving the child living and administration of his/her drugs and also who brought the child to the follow up. The person could change over time.

Adherence: for this study the report of the status of adherence on ART follow up chart was used Participants were classified as

1. Good adherence: are those with good adherence documented throughout the follow up
2. Faire - Those patients with one episode of poor adherence documented
3. Poor adherence: More than two episode of poor adherence documented

4.12 Ethical consideration

Ethical approval was sought from University of Gonder and Addis Continental Institute of Public Health and from Alert review committee .The study institutions were informed the purpose of the study through supporting letter from UGACIP and the Addis Ababa Regional Health Bureau Bero. Confidentiality of patient information was kept by the investigator and data collectors and names of the patient and patient information was omitted from the structured questionnaire. Personal data obtained was accessible to primary investigators and was stored in secured area. The confidentiality will still be kept in dissemination of the result as well. Due to the retrospective and chart review nature of the study; informed consent was gained from each hospital rather than individual patients (Annex II and Annex III).

5 Result of the study

The number of patients who were on first line ART for at least six months and less than 15 years of age were 1,220 from which 1,186 Pediatric patients were studied and 34 were excluded because of incomplete documentation. From the 1,186 in the sample, 608 (48.8%) are female while 578 (51.2%) are male. The mean age at initiation of ART was 74.6±37.3SD months and range (2 -172) months. The primary care takers were both parents for 35% of the patients while only one of the parents (either mother or father) in 33.7%. Percentage of patients under the care of relatives is 10.5%, Orphanage and guardians were 8.3 and 12.0% respectively. Nearly 25 % of children lost there both parents and 43.45 % of them either parents. Only 2.4% of children had PMTCT and received infant prophylaxis (Nvp only 0.8% and NVp+Zdv 1.6%) see Table 4.

Regarding the base line data during initiation of ART nearly 71% of the patients were in WHO clinical stage III and IV while those in stage I and II were 3.5% and 25.7% respectively. Severe and advanced immunologic deficiency at the time of start was found in71.9%. The reason for the start of ART was WHO clinical staging in 210 (17.7%), CD4 count in 248 (20.9%) and both WHO and immunologic for 719 (60.6%) of the patients and 9(0.7%) of the patients age less than one year was used as a criteria to start ART. The regimen type initiated at base line was Neverapine based in 688 (58%) and Efaverense based 467(39.3%) see Table 4.

Table 4: the socio Demographic and clinical characteristics of children on HAART in selected Hospitals of Addis Ababa, 2011.

Characteristics	Number (%)
Age	
≤ 11 months	46( )
11 to 34	169 (14.2)
34 to 59	212 (17.9)
≥60 month	759 (64)
Sex (n=1186)	
Female	608 (48.8%)
male	578 (51.2%)
Hospital (n=1186)	
Alert	215(18.1)
yekatit	252 (21.2)
Tikur Anbessa	404 (34.1)
Zewditu Memorial	315 (26.6)
Parental status n=1155	
Both alive	427(36.96)
Either dead	468(40.51)
Both dead	260(22.5)
Primary care taker	
Both parents	415(35)
Mother	249(21)
Father	156(13.2)
Relatives	125(10.5)
Guardians /neighbors	142(12)
Orphange	99(8.3)

Characteristics	Number (%)
Serology of the care takers	
Positive	773(65.2)
Negative	55(4.6)
Unknown	358(30.2)
Parental status	
Both alive	
Either dead	
Both dead	
WHO stage(n=1186)	
I	42(3.5)
II	305(25.7)
III	626(52.8)
IV	213(18)
Regimen started initially	
4a(DRT+3TC+NVP)	388(32.7)
4b(DRT+3TC+EVS)	106(8.9)
4c(AZT+3TC+NVP)	300(25.3)
4d(AZT+3Tc+Evs)	361(30.4)
Other	31(2.6)
Infant ART prophylaxis	
NVP	9(0.8)
NVP+ZDV	19(1.6)
None	977(82.4)
Unknown	181(15.3)
Tb after ART (n=1186)	36(3%)

A significant number of children were malnourished at base line that is weight for age, height for age and weight for height was less than -3zs for 14.5%, 27.9% and 2.4% of the patients respectively .During the start of ART 400(33.7%) children were having sever immunodeficiency State based on either CD4 percentage in under 5 or CD4 count in above 5 year of age. The CD4 count was less than 50 in 80 (6.74%) of all children see Table 5.

Table 5: Socio-demographic and clinical characteristics of treatment failures and treatment success groups in children on HAART in Addis Ababa, 2011

Covariant	Treatment failure Number	Treatment success number	Crude HR (95%CI)	Adjusted HR (95%CI)
Age (month)				
age ≤11	9(5.4)	37(3.6)	1.036(0.504-2.128)**	
age 11-34	36(21.6)	131(12.9)	1.13(0.724-1.764)	
age 35-59	29(17.4)	190(18.2)	0.632(0.393-1.015)	
age: 60 to 108	51(30.5)	473(46.9)	0.454(0.301-0.685)**	
age> 109	42(25.1)	193(18.9)	1	
Sex (n=1186)				
Female	71(42.5)	506(49.7)	0.785(0.577-1.069)	
male	96(57.5)	512 (50.3)	1	
Primary care taker				
Both parents	65(38.9)	350(34.3)	1.113(0.635-1.952)	
Mother	28(16.8)	221(21.7)	0.768(0.410-1.438)	
Father	26(15.6)	130(12.8)	1.049(0.553-1.990)	
Relatives	18(10.8)	107(10.5)	0.937(0.472-1.859)	
Guardians/neighbours	15(9)	127(12.5)	0.709(0.346-1.450)	
Orphanage	15(9)	84(8.2)	1	

Covariant	Treatment failure Number	Treatment success number	Crude HR (95%CI)	Adjusted HR (95%CI)
Sero status of care takers				
Positive	112(67.1)	661(64.9)	1.122(0.798-1.578	
Negative	8(4.8)	47(4.6)	0.94(0.409-2.001)	
Unknown	47(28.1)	311(30.5)	1	
Adherence level				
Good	162(97)	1006(98.7)	0.450(0.111-1.814)	
faire	3(1.8)	8(0.8)	0.843(0.141-5.052)	
poor	2(1.2)	5(0.5)	1	
Weight for age at ART0				
≤-3zs	52(31.5)	120(11.8)	2.385(1.024-5.553)*	
_-3zs -+3zs	107(64.8)	856(84.4)	0.813(0.357-1.852)	
≥3zs	6(3.6)	38(3.7)	1	
Height for age at ART)				
≤-3zs	88(53.7)	239(23.7)	2.223(1.156-4.276)*	0.429(0.291-0.632)**
-3zs -+3zs	66(40.2)	697(69.2)	0.653(0.336-1.271)	
≥ +3Zs	10(6.1)	71(7.1)	1	
Weight for height NCHS				
>-1Zscore	6(4)	20(2.2)	1.926(0.844-4.404)	
-1to -2Z score	9(6)	70(7.7)	0.927(0.468-1.937)	
<-2Z score	41(27.5)	204(22.5)	1	
<-3 Zscore	93(62.4)	614(67.6)		

Covariant	Treatment failure Number	Treatment success number	Crude HR (95%CI)	Adjusted HR (95%CI)
WHO clinical stage on HAART initiation				
Stage 1	7(4.2)	35(3.4)	1.324(0.587-2.984)	
Stage 2	46(27.5)	259(25.4)	1.059(0.681-1.644)	
Stage 3	79(47.3)	547(53.7)	0.809(0.543-1.205)	
Stage 4	35(21)	178(17.5)	1	
CD4 % or count at ART start				
Sever immunodeficiency	67(41.9)	383(41.4)	0.711(0.464-1.089)	
Advanced immunodeficiency	43(26.9)	288(31.1)	0.652(0.411-1.035)	
Mild immunodeficiency	19(11.9)	126(13.6)	0.620(0.350-1.098)	
No immunodeficiency	31(19.4)	129(13.9)	1	
CD4 at initiation				
>50	112(85.5)	859(93.4)	1.930(1.173-3.176)*	2.009(1.194-3.380)**
≤50	19(14.5)	61(6.6)		
PMTCT for mother				
Present	3(1.8)	21(2.1)	1.268(0.394-4.086)	
None	119(71.3)	705(69.2)	1.196(0.848-1.687)	
unknown	45(26.9)	293(28.80	1	
Disclosure				
Disclosed	41(36)	270(35)	0.971(0.660-1.428)	
Not disclosed	73(64)	501(65)	1	

Covariant	Treatment failure Number	Treatment success number	Crude HR (95%CI)	Adjusted HR (95%CI)
ART infant prophylaxis				
NVP only	1(0.6)	8(0.8)	1.454(0.194-10.896)	
NVP+ZDV	4(2.4)	15(1.5)	2.99(1.010-6.849)*	
None	144(86.2)	833(81.7)	1.720(1.053-2.810)*	
HAART regimen type				
4a(DRT+3TC+NVP)	59(35.3)	329(32.3)	0.453(0.232-0.886)*	
4b(DRT+3TC+EVS)	14(8.4)	92(9)	0.347(0.154-0.782)*	
4c(AZT+3TC+NVP)	46(27.5)	254(24.9)	0.377(0.190-0.749)**	
4d(AZT+3Tc+Evs)	38(22.8)	323(31.7)	0.245(0.122-0.493)**	
other	10(6)	21(2.1)	1	
Substitution of single drug				
Present	138(82.6)	94(9.2)	0.501(0.336-0.0.748)**	1.695(1.053-2.728)*
Absent	29(17.4)	925(90.8)	1	
Dose form				
Fixed	9(5.4)	42(4.1)	1.268(0.394-4.086)	
Separate	109(65.3)	600(58.9)	1.196(0.848-1.687)	

The mean follow up period after ART initiated was 37±17month with minimum 6month to maximum of 74months. Though high number of malnutrition observed at base line; a marked increase in weight for height observed after 12 month of ART see Fig 2 and 3.

Figure 2: weight for height at ART initiation month compared to the WHO Standard curve

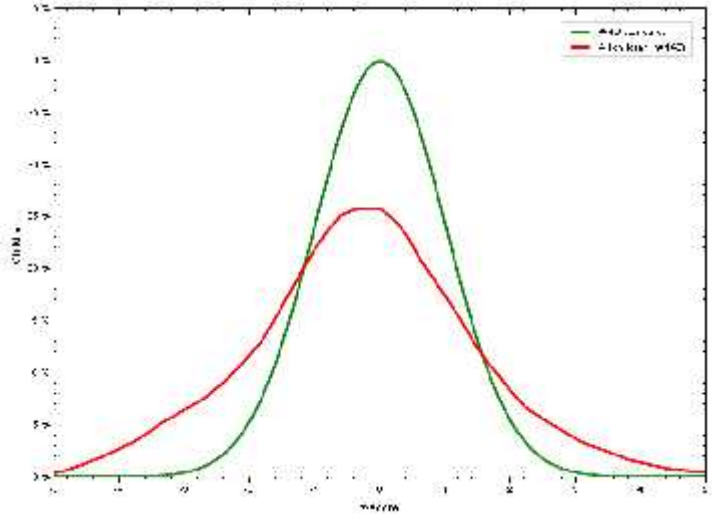
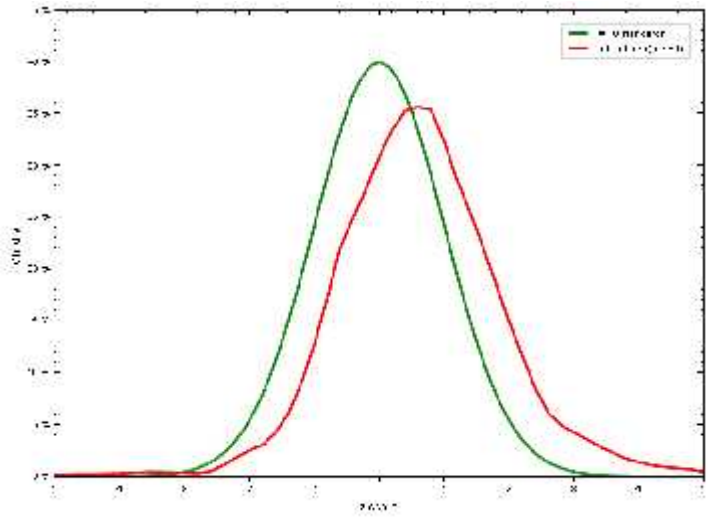
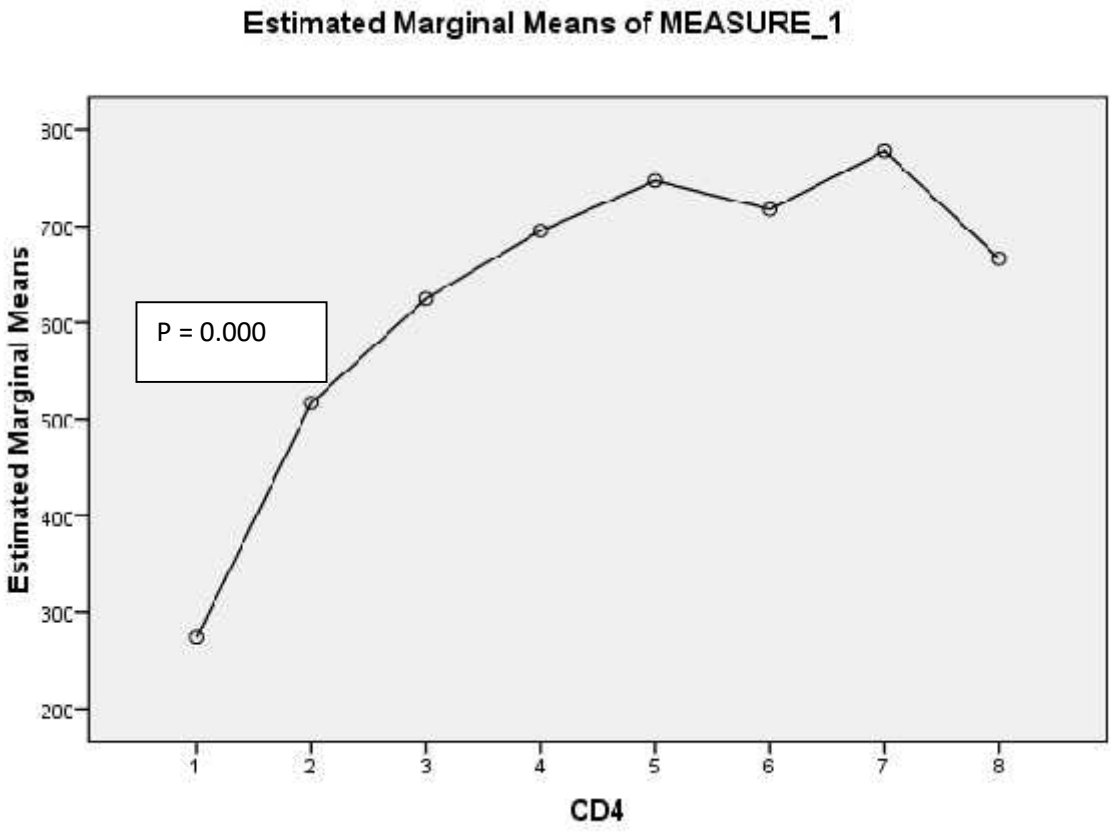


Figure 3: weight for height after ART 12 month compared to the WHO standard curve



Similarly though large number of children were having sever immunodeficiency at base line the mean increment CD4 count is statically significant till 12 month after ART(p=0.000) then it slops till 36 month of ART with no statistically significant increment in CD4 and then start to decline after 42 month this is although it was not a statically significant decline p=0.48 Fig 4

Figure 4: The mean CD4 count over 42 month of follow up.



Over all opportunistic infection incidences after the start of ART was 52 (4.4%) the mean onset was (20.79-±15.914) months and the range(2month to 62 month) and the commonest Opportunistic infection being Tb in 36 (3%), 16(1.3%) chronic diarrhea more than two weeks, 2 of the patients had peumocystic carina pneumonia, 2 recurrent intractable oral thrush , 1 recurrent severe pneumonia .

The overall adherence report was good; with no episode of poor adherence being in 98.4% and two or more episode of poor adherence was documented in 7 (0.6%) of the patients.

Anti-retroviral drug substitutions were done for 119 (90%) patients. The majority of substitution was done for toxicity 94 (7.9%), 7(0.6%) for concomitant TB treatment, and for 4 (0.4%) patients the causes of substitution were not specified.

Out of the 167 patients 80 (%) developed clinical treatment failure, 87(52%) of them immunologic failure and 18 (10.77%) developed both immunologic and clinical failures. Clinical failures due to developmental regression were 22(1.9%),due to growth failure and opportunistic infection were 51(4.3%) an 35(3%) respectively.

Patients who had height for age greater than -3 z-score (ZS) with (AHR) of 0.429 95%CI(0.291-0.632) were found to have less probability of treatment failure see figure 5. Compared to the Patients with base line CD4 count above 50 those who had below 50 h higher probability of treatment failure (AHR=2.009(1.194-3.380)) see Fig 6; Similarly the presence of chronic ve diarrhea after start of ART (AHR= 3.439(1.372-8.623)) and with drug substitution (AHR=1.695(1.053-2.728)) were also found to be at risk.(Fig 7 and 8)

Figure 5: Cumulative probability of not having treatment failure in HAZ Categories

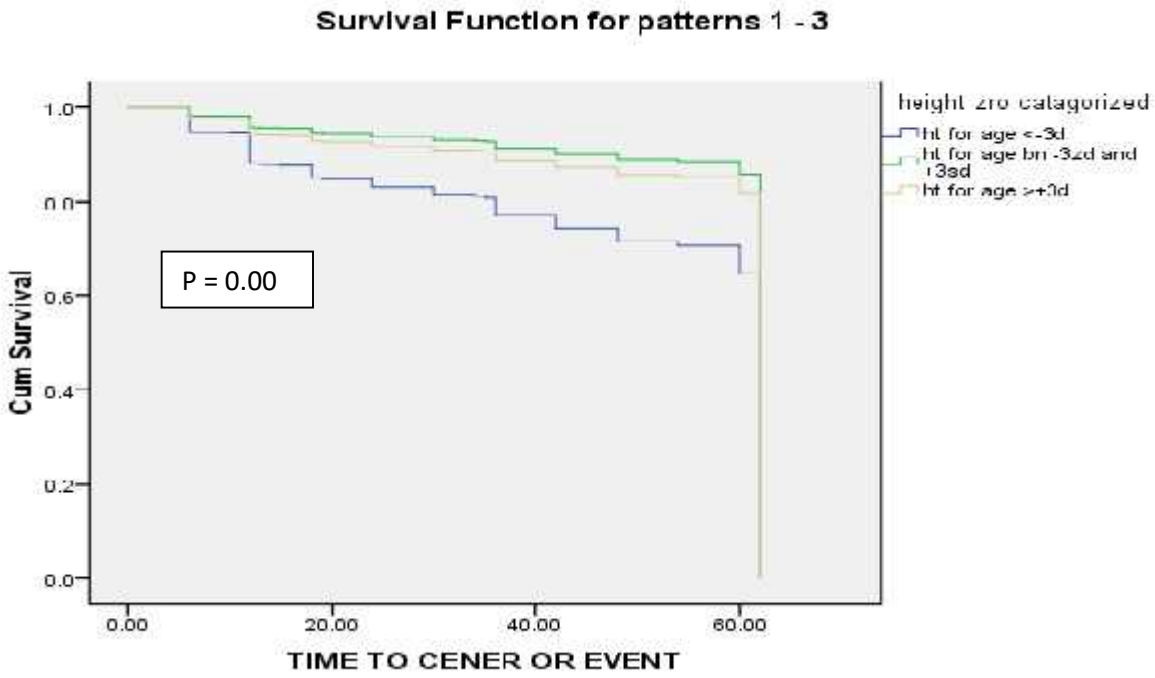


Figure 6: Cumulative probability of having treatment failure with CD4 count less than 50

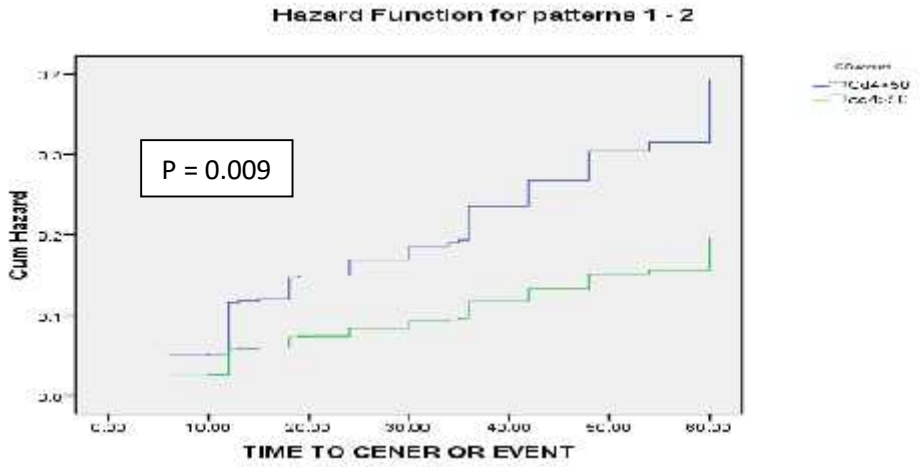


Figure 7: cumulative probability of treatment failure in Children where chronic diarrhea present or absent after ART initiation

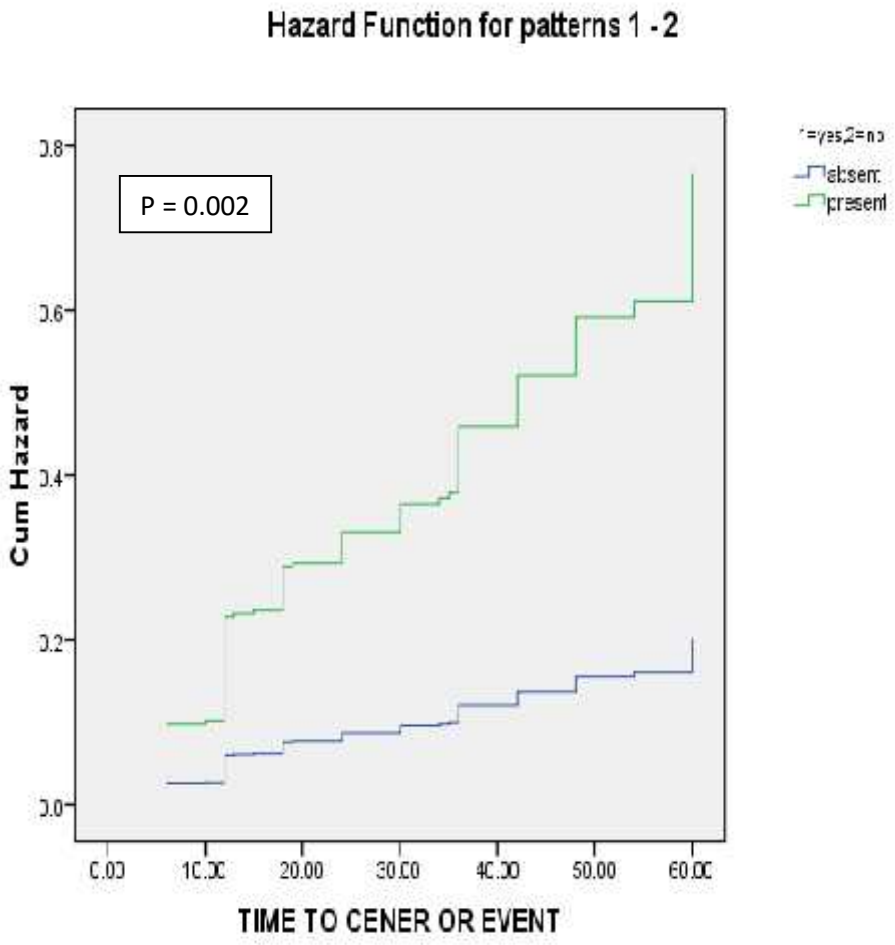
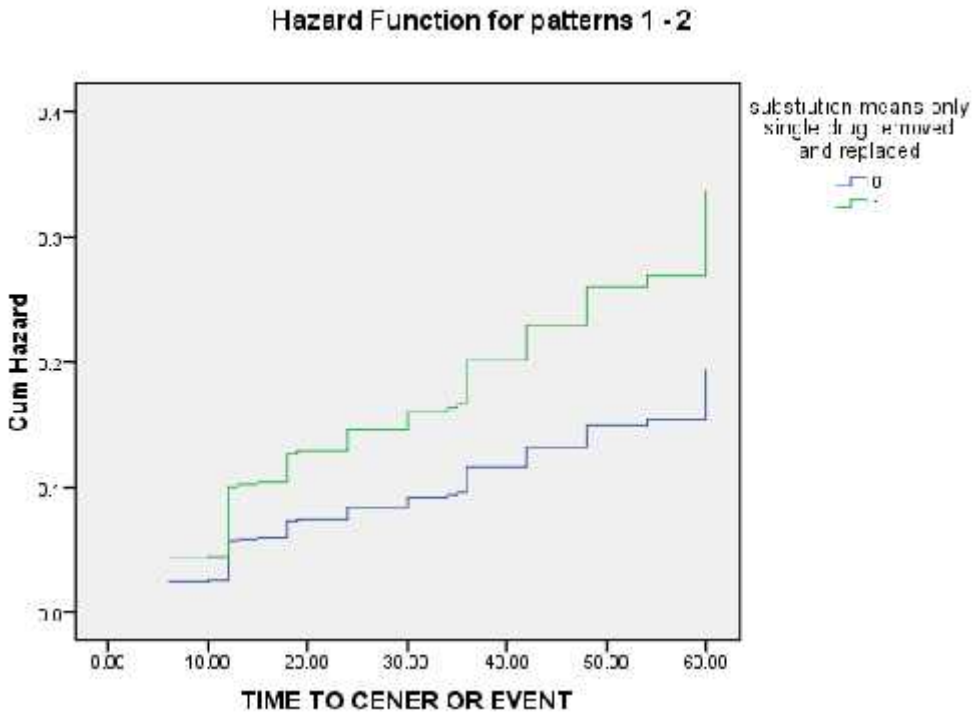


Figure 8: The cumulative probability of having treatment failure with and with drug substitution



When we see the detection rate of treatment failure out of the 167 only 24 (i.e14.35%) treatment failures were identified. The mean of treatment failures from the time ART started was 19.7 (± 14SD) months and the duration of time from treatment failure to second line for those switched was 24±31.67month..

Table 6: First line Treatment failures vs. switch to second line

Time of Treatment failure		
	Number of Treatment failures with first line	Treatment switched to second line
Number	143	24month
Mean duration till failure /switch	19.7(± 14SD)month	24±31.67month
Range	6-62 month(±16.7)	5-7month

6 Discussions

This study found higher number of treatment failure patients (14.1% out of 167) clinical failure are observed in 80(7%) and immunologic failure in 87(7.3%) and both in 18 (1.5%). only 24 of them are labeled as treatment failure and switched to second line. This is in contrary to the national report of only 135 pediatric patients put on second line drugs (6, 7, 41).This finding demonstrates that a significant number of treatments failures are not identified and/or not switched to second line.

The overall sex distribution is slightly higher for females than males (51.15 %vs 48.8%) this is similar to the finding of the study in Jimma University (31). Although the Makerere University and Chiang Mai, Thailand study which showed male sex as predictor of treatment failure , this was not demonstrated in our study(20,30,). Similar to the Mekrere university which found younger age was commented as a predictor of virologic failure, in our study the age group <11month have higher risk than their older age counterparts (20, 30,34,40) on bivariat cox regression but not demonstrated in multivariate analysis . Unlike the Jimma and the Cambodian studies, there was no association of treatment failure was identified with being an orphan (18, 31).

Only 2.4 %(ie 0.8% took NVP only and 1.6% NVP+ZDV) for infant prophylaxis which could be explained by the low Antenatal coverage 28% and institutional deliveries of the country (5%). (7). Most of these HIV infections could have been prevented if these children had PMTCT service. The majority of patients were having WHO stage 3 and 4 in 70.8% at initiation unlike the Study in Jimma WHO clinical staging didn’t show increase in probability of treatment failure (31).

Adherence in this study didn't show a statically significant difference in predicting treatment failure this could be due to the good report of adherence in this study i.e. 98.5% .But a crossectional study conducted in the same hospitals previously showed adherence report by care giver in the past 7 days before the interview was (86.9%) .Looking this data the adherence reported on the charts in our study might be not reliable. (22)

Fifty two (4.4%) of our patients developed OI which is less than the report in Jimma which was 7.3%.This could be the result of high lost in follow up in Jimma . similarly a cohort study in two district hospitals of Cambodia showed the OI incidence declined from 14.4 %Pre HAART to 1.1 cases per 100 patient-years with HAART (18).The US Perinatal AIDS Collaborative Transmission Study demonstrates the time of onset and incidence of bacterial OI has shown a decrease trends in the in the post HAART era than the pre HAART era (12). Similarly study showed the rate of hospitalization markedly decreased in HAART era (13).

Anteretroviral drug substitutions were done in 119(ie10%) of all children studied. The majority reason for substitution was toxicity for 94 (7.9%) patients .This is similar to the study in Jmma (31) Patients who had substitution were in a higher probability of failure(AHR=1.695(1.053-2.728)). This is similar to the Malawi study (26). This shows interruption of drug for toxicity will lead to viral replication which intern result in treatment failure.

This study showed a significant association of treatment failure patients with chronic diarrhea after ART initiation (AHR= 3.439(1.372-8.623)) this association also seen in Jimma study relation (31) but they studied diarrhea at the time of initiation where as ours is after the ART started. This study also showed a significant increase in the occurrence of treatment failure with baseline chronic malnutrition .This finding is in consistence with the study Tan Tock Seng Hospital, Singalinepore where they found hazard ratio (HR) 2.19, 95% CI (1.29-3.73) P=0.004 for those with BMI<17 at base line and also the Jimma retrospective cohort showed 12.7(1-154.5) P=0.06. (36, 40) for acute malnutrition at the start of ART (31,38)

Regimen type didn't predict treatment failure in our study in contrary to the Uganda study where the independent viral failure in children was stavudine (d4T)/lamivudine (3TC)/Nevirapine (NVP) versus zidovudine (ZDV)/3TC/efavirenz (EFV) with odds ratio [OR] = 2.59, 95% CI (1.20 to 5.59); Other studies showed also Efavernce based vs Nevirapine based predicts treatment failure but this also was not demonstrated In our study (20,34,35).

When we see the case detection rate 0f treatment failure it was low 24 (i.e14.35%) treatment failures. The mean duration of treatment failures still on first line is 19.7 (± 14SD) months and the duration of time from treatment failure to second line for those switched was 24±31.67month. Compared to the retrospective study in Malawi this time is less, where the average time on ART before shifting to second-line ART regimen was reported 16.3 months. But compared to the South Africa where the median time between virologic failure and switch was 4.6 months our study showed a delay in time of shift (26).

7 Strengths of the Study

- This is the first large scale study which studied treatment failure in Ethiopia.
- Major public pediatric referral hospitals were included.
- Data quality was assured by using Nurses trained in ART as data collectors

8 Limitations of the Study

- Deaths and transferred out were not considered
- Retrospective nature of the study limits the important variables like seeing drug interaction as treatment failure.
- Poor documentation variables made it impossible to see the effect of poor dose adjustment for the weight of a child
- The effect of inttercurrent illness on CD4 couldn’t be controlled

9 Conclusion and Recommendation

Conclusion

- chronic malnutrition at base line at base line was found to be a predictor of treatment failure
- Chronic diarrhea after the start of ART associated with increased probability of having treatment failure.
- Substitution of drugs for toxicity was found to increase the risk of having treatment failure.
- Children who were having very CD4 less than 50 at base line were having increased treatment failure probability.
- Sex , WHO clinical stage , disclosure status was not found to predict risk of treatment failure adherence showed association among failure and non failure but it was not statically significant.
- Majority of treatment failure patients were not detected and a significant delay in switching to second line from the time of treatment failure identified.

Recommendation

- Prevention and treatment of children with malnutrition should be done in pre ART for all children living with HIV
- Early initiation of treatment before sever immunosuppression is mandatory
- Prevention of chronic diarrhea with good personal hygiene, proper disposal of wastes and identifying the cause of it and treating early is recommended
- Children who require substitution of drugs should be closely observed for possible treatment failure and delay in restart of the treatment should be minimized
- Early detection of treatment failures and timely switch tom second line is important
- Further prospective study is recommended to see the out come of those in second line drugs.

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Annexes

Annex I. Data collection Format

I. Patient identification

1. Facility Name

2. Patient card number

3. Unique Art number

II. Socio demographic Factors:

Number	Question	Response category	Code
4	Age	Month ….	
5	sex	1.Female 2.Male	
6	Primary care taker	1) father 2) mother 3) grand parent 4)sibling 5)relative 6)neighbor 7) orphanage 8) other	
7	Serology of care giver	Positive Negative unknown	

III. Clinical feature of patient:

Anthropomethry

Number	**Month after Art started**	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**52**	**Code**
8	**Wt**											
9	**Ht**											
10	**HC**											

Number	**Question**	**Response category**	**Code**
11	Date of confirmation of Hiv status	Date /moth/year	
12	Previous PMTC for infant	1) yes 2) No 3) unknown	
13	If yes on q 12	NVP NVP and AZT	
14	ART prophylaxis for PMTCT the mother	SNVP SNVP +AZT none	
15	Type of HIV TEST	a)Rapid HIV (for >18month) or Elsa c) Pcr less than 18 month	
16	Who stage on Art initation	1)I	

		2)II 3)III 4)IV	
17	Date of ART started	Date/moth/year	
18	Reason for starting ART initation	1) WHO STAGE 2) Immunolgic only 3) A and b 4) Virologic 5) A, b ,and c 6=the age of the child is <1year	
19	Type of ART	1=4a (DRT +3Tc +NVp) 2=4b (D4T+3Tc + EVs) 3=4c(AZT + 3TC+ NVp) 4=4d(AZT+3Tc +EVs) 5=kaletra based /other	
20	Dose form	1) syrup 2) tablet 3) both used at different times	
21	Drug form type	1) fixed dose combination 2) separate 3) both used previously	

22	Was any time the Art drugs substituted	1.yes 2.No	
23	Drug substitution reason	1)Toxicity 2)Failure 3)Other diseases like tb 4)Age 5)Other reason 6)Not specified	
24	If on Q23 Drug substitution reason date	Date/Mon/year of switch	
25	If Q 23 is yes to which regimen changed refer 19		
26	New OI	1) Yes 2) No	
27	Tuberculosis after start of ART if yes what type	Yes No	
28	If Q 26 yes	1) Pulmonary 2)Extrapulmonary 3) Disseminated tb	

29	Treatment failure	1)yes 2)No	
30	If question number 27 is yes	1) Who stage back ward 2) growth failure despite nutritional support 3) developmental regression /delay 4) new or recurrent OI	
31	Treatment failure	clinical Immunologic Virologic 1 and 2 2 and 3 1 and 3 1,2,3	
32	Chronic diarrhea or persistent diarrhea	1. Yes …… 2.No……	
33	If Q 30 yes	if yes duration	
34	Disclosure done:	1) yes , 2) no 3) not applicable if age <8 4) not documented	
35	Developmental milestone	1)appropriate 2)Delay	

		3)Regression 4)not documented	
36	Switch to second line	1)yes 2)No	
37	Date of swich	Date/month/year	

IV. Laboratory and adherence

Month	At Art start	6	12	18	24	30	36	42	48	52	code
CD4 number if child is > 5years											
CD4 % is less than 5year											
Immunologic category at initiation of therapy											
Adherence report eof the cumulative 6 month											

Annex II: Consent Form

This is a study conducted for partial fulfillment of a post graduate program requirements at University of Gondar and Addis Continental Institute of Public Health joint MPH Program. The main objective of this study is to assess the magnitude of first-line ART failure and its predictors among HIV-infected pediatric patients on ART registered at major public pediatric referral hospitals in Addis Ababa. Such assessment will help identify potential challenges for program's success and provide useful information for designing interventions against the challenges. It will also help in providing an insight to the program's performance and clients' follow up status in the hospital. Therefore, the hospital's participation and collaboration is very much helpful in generating the required information and will be very much appreciated.

In this study data will be collected from the Pre-ART, ART registers and follow up forms using a form developed for this study. Information regarding socio demographic characteristics, clinical and laboratory data, follow up status and information on outcomes of each client in terms of first-line ART failure will be collected from the registers. Information regarding any specific personal identifiers like the name of the clients will not be collected and information generated will be disclosed in totality. In addition, confidentiality of any personal information will be maintained throughout the study process and no unauthorized access to the information is allowed.

Finally, the hospital has all the right to refuse to participate in this study and shall withdraw from the study at any time. If they have any questions or need further information regarding the planned study you are free to get clarifications the principal investigator or from the institution or through the following addresses; Addis Continental Institute of Public Health, Tell 0116526853 (Dr. Alemayehu Worku – the primary advisor of this research) or Dr Tigist Bacha, Tell.0911676304 (the principal investigator).Therefore, if you would like to participate in this study, would you please confirm it by signing here . Thank you very much

Participant: ---------- Principal investigator: ----------

Annex III

የፋቃደኝነት መጠያቅያ ቅጽ

ይህ ጥናት በጎንደር ዩንቨርሲቲ ና በአዲስ ኮንትኔን ል የማህበረሰብ ጤና አጠባበቅ ኢንስቲትዩት ጋር በመተባበር ለድህረ ምረቃ የመመረቂያ ፅሁፍ ነው ::

የጥናቱ ዋና አላማ በአዲስ አበባ በሚገኝ የመንግስት ሆስፒሎች የተመዘገቡ ከኤች አይ ቪ ጋር አብረው በሚኖሩ ህፃናት ላይ ያተኮረ ሲሆን አላማውም በመጀመሪያ ደረጃ የሚሠጡ የፀረ ኤች አይ ቪ መድኃኒት ክሽፈት መጠንን ማጥናት ሲሆን ና የክሽፋቱ ለሚያመጡ የችግሩ አመላካች ምክንያቶችን ማጥናት ነው ::

ይህ ጥናት ለተለያዩ በኤች አይ ቪ ላይ ለሚሠሩ የስኬት ፈ ኝ ሁኔ ዎችን ለመለየት ና ንዲሁም ለፈ ኝ ሁኔ ዎቹ መፈትሄ ለመቅረፅ የሚረዱ መረጃዎችን ለመስጠት ነው :: ስለዚህ ተፈላጊ መረጃዎችን በመሰብሰብ ሥራ ላይ የሆስፒ ሎቹ ተሣትፎና ትብብር በጣም የሚደገፍ ነው ::

በዚህ ጥናት መረጃዎች የሚሰበሰቡት የቅድመ ፀረ ኤች አይ ቪ ህክምና መድሀኒት ህሙማን ከመወሰዳቸው በፊት ከሚመዘገብበት መዝገብ ላይ ና ሲጀምሩ ና ከጀመሩም በኋላ በሚመዘገቡት መዝገብና ካርድ ተወስዶ ለዚህ በተዘጋጀ ፎርም ላይ ይሰበሳበል::

የሚሰበሰበው መረጃ ይዘት የ ማሚውን የማህበረዊና የጤንነት ሁኔታ እና የላብራቶሪ መረጃዎችን የክትትል ሁኔታ የህክምና ውጤት ደረጃና ከየመዝገቦቹ ይካተታሉ:: ተማሚው የግል ገላጭ የሆነ ማለትም የበሽተኛው ስም በመሰብሰብያ ወረቀት ላይ አይሰፍርም:: በጥናቱ ውጤት የሚገኘው መረጃ በግለሰብ ደረጃ ሳይሆን በአጠቃላይ ይፋ ይሆናል:: የበሽታኞች ምስጥር በሙሉ በድብቅ በጥናቱ ቆይታ ሂደት ሁሉ እንደተጠበቁ ይቆያሉ በጥናቱ እንዲሰሩ የልተካተቱ ሰዎች መረጃዎችን እንዲያገኙ አይፈቀድላቸውም::

በመጨረሻም የሆስፒታሎቹ ሙሉ ለሙሉ በጥናቱ ላይ ላለመሳተፍ መብት አላቸው፡፡ በጥናቱ ሂደት መዕከልም የማቋረጥ መብት አላቸው ለማንኛውም ጥያቄና መረጃ ጥናቱን በተመለከተ ከጥናቱ ዋና አማካሪ እንዲሁም ከጥናቱ ዋና አጥኝ ወይም ከአዲስ ኮንትኔታል እኒስቲትዮት ከታች በተዘረዘሩት አድረሻዎች ለመነጋገር ማብራሪያ ማግኘት ይችላሉ፡፡

ዶ/ር አለማየሁ ወርቁ /ዋና አማካሪ / 0116526853

ዶ/ር ትዕግስት ባጫ /ዋና አጥኝ/ 0911676304

በዚህ ጥናት ለመሳተፍ ፈቃደኛ ከሆኑ እባክዎን በፊርማዎ የረጋግጡ

ከምስጋና ጋር

Annex IV. Declaration

I, the undersigned declare that this thesis is my original work in partial fulfillment of the requirement for the degree of Master of Public Health. I also declare that it has never been presented in this or any other university and that all resources and materials used in the thesis have been duly acknowledged.

Student Name: _____

Signature: _____

Place of submission: _____

Date of submission: _____

This thesis has been submitted with my approval as a university advisor.

Advisor Name: _____

Signature: _____

Date of submission: _____